REMARKS

This communication is responsive to the Office Action mailed in the above-captioned application on March 27, 2002. Claims 1-8 are pending. Claims 9-36 have been canceled. Claims 1 and 5 have been amended.

Upon entry of this amendment, claims 1-8 will be pending. Independent claims 1 and 5 have been amended to recite the limitation, "wherein said LHRH comprises a C-terminal fragment of at least five amino acids." Support for the recitation "wherein said LHRH comprises a C-terminal fragment of at least five amino acids" in amended claims 1 and 5 is found in the abstract, at page 1, lines 5-6 and page 8, line 6 of the instant specification.

Claims 9-36 have been canceled because they are drawn to a non-elected invention. Applicants reserve the right to pursue the subject matter of the canceled claims in subsequent applications. The cancellation of claims does not constitute acquiescence in the propriety of any rejection set forth by the examiner.

The specification has been amended to reflect the relationship between the instant application and PCT/AU98/00532 as required by the Examiner. The specification has also been amended to comply with the Examiner's objection to the arrangement of the specification. These amendments do not contain any new matter.

Rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph

Claims 1-8 are rejected under 35 U.S.C. § 112, first paragraph. Applicants respectfully traverse this rejection. "The examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed..." USPTO Guidelines for Examination of Patent Applications under Section 112, Fed. Reg. 66(4):1099-1111. The Examiner has not explained the alleged written description deficiencies in sufficient detail.

The Examiner asserts that the specification does not reasonably provide a written description of *any* composition comprising *any* LHRH conjugated to diptheria toxoid and an ionic polysaccharide where said LHRH is *any* LHRH 2-10 form or any modified LHRH 2-10 form. The Examiner further asserts that the written description is only sufficient to support claims directed to a composition comprising a human LHRH-diptheria toxoid conjugate wherein said human LHRH consists of SEQ ID NO: 1, LHRH 2-10 form consisting of SEQ ID NO: 2 or a modified human LHRH consisting of SEQ ID NO:4 and an ionic polysaccharide, wherein said ionic polysaccharide is DEAE-dextran together with one or more pharmaceutically acceptable carrier and/or diluents. Office Action at page 4.

In the present case, the examiner has not met the burden of presenting the evidence required to establish a rejection for lack of written description. The written description requirement ensures that the skilled artisan would understand, based on the specification, that the inventor possessed the claimed invention at the time the application was filed. *Vas-Cath v. Marhurkar*, 935 F.2d 1555, 1564 (Fed. Cir. 1991). Literal correspondence between the claims and the specification is not required. *See In re Wertheim*, 541 F.2d 257, 265 (CCPA 1976). Furthermore, breadth alone is not sufficient basis for rejecting claims under the written description requirement. The Examiner is required to set forth, with specificity, the reasons for the rejection. See Fed. Reg. 66(4):1106-1107 (2001).

In the instant case, the claims set forth, with structural detail, recitation of the structural features of the claimed invention. "Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." Fed. Reg. 66(4):1106 (2001).

The Examiner asserts that the specification does not provide sufficient written description for the claim limitation "ionic polysaccharide." One of ordinary skill in the art would readily understand what is encompassed by this claim limitation. Numerous ionic polysaccharides with defined chemical properties are known in the art. The specification specifically defines ionic polysaccharide as "any positively or negatively charged polysaccharide or derivative or chemical equivalent thereof." Page 4, lines 15-

16. The specification also enumerates species of ionic polysaccharides, such as "DEAE-dextran, dextran sulphase or QAE-dextran." Page 4, lines 20-21. The disclosure in the specification in combination with the extensive knowledge in the prior art regarding the types and physical characteristics of the genus of ionic polysaccharides provides sufficient written description of this claim element.

The Examiner also asserts that the specification does not provide sufficient written description for a "LHRH-diptheria toxoid conjugate." Applicants respectfully disagree. Nevertheless, to expedite prosecution of the present case, and without acquiescing to the position of the Examiner, independent claims 1 and 5 have been amended to recite "wherein said LHRH comprises a C-terminal fragment of at least five amino acids." Applicants maintain that the amendments were not made for purposes of patentability, but were made to expedite prosecution.

The specification provides sufficient written description for an LHRH-diptheria toxoid wherein said LHRH comprises a C-terminal fragment of at least five amino acids. Given the small size of the LHRH protein and the fact that many LHRH and derivatives thereof are known, one of ordinary skill in the art would easily recognize the amino acid sequence of LHRH and its derivatives. Furthermore, it is well known that any LHRH fragment comprising at least five amino acids is immunogenic when conjugated to a carrier protein.

For example, the LHRH 1-10 form has been shown in the prior art to induce an immune response. *See, e.g.,* WO88/05308, example 30 (Appendix A). *See also,* Fraser *et al.*, *J. Endocrinology*, 61:ix-x, 1974 (Appendix B). Additionally, the immunogenicity of the 3-10 form of LHRH is also well known and has been extensively described in the prior art. *See, e.g.* Fraser *et al.* at x ("Fourteen rats have been used to raise antisera to the 3-10 octapeptide. All have produced antibody which cross-reacts with LH-RH *in vitro*."). Finally, WO88/05308 describes the vaccination of animals with an immunogenic protein conjugated to a peptide selected from the group comprising any continuous 5, 6 or 7 amino acid fragments of the LHRH decapeptide, which includes the 4-10, 5-10 and 6-10 forms of LHRH. WO88/05308, Examples 26-30 and 34. The data demonstrate that these forms of LHRH are all immunogenic. *Id.*

The present invention is predicated on the determination that the efficacy of vaccination against LHRH is significantly improved when the LHRH molecule, or fragment thereof, is administered as a conjugate together with diptheria toxoid and an ionic polysaccharide. Although the improved efficacy of the LHRH formulation of the present invention has been demonstrated using the LHRH 2-10 form or a modified LHRH 2-10 form, any LHRH fragment of at least five amino acids that demonstrates immunogenicity and is therefore suitable for use in the method of the present invention. The instant invention will, by virtue of its unique formulation, improve the efficacy of any LHRH fragment of at least five amino acids. The invention does not lie with the specific form of LHRH which is utilized, but rather with the manner of its formulation. In this regard, the present specification provides detailed description in relation to the issue of formulation. Because it is not the immunogenicity of the LHRH fragment which forms the subject of the invention, but rather the improved efficacy which can be obtained by utilizing the subject fragment in accordance with the formulation detailed in the specification, it is respectfully submitted that the written description requirements are satisfied.

Moreover, to the extent that the rejection is based on alleged indefiniteness, a claim need only reasonably apprise those skilled in the art of the utilization and scope of the invention to meet the statutory requirement for definiteness. *Hybritech, Inc. v. Monoclonal Antibodies*, 231 USPQ 81, 94-95 (1986). Each member of the claimed genus need not be recited for the claim to be definite within the meaning of §112, second paragraph.

Withdrawal of the rejection of claims 1-8 is respectfully requested.

Rejection of claims 1-8 under 35 U.S.C. § 103(a)

Claims 1-8 are rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Pat. No. 5,378,688 or Sad *et al.* (Immunology 74:223-7, 1991) each in view of U.S. Pat. No. 5,614, 487 or U.S. Pat. No. 5,403,586. Specifically, the Examiner asserts that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the diptheria toxoid conjugate for a contraceptive vaccine as taught

by the '688 patent or substitute the alum as taught by Sad *et al.* with the drug carrier such as polysaccharide dextran as taught by the '487 or the '586 patents." Office Action at page 6. Rejection of the claims is respectfully traversed.

To establish a *prima facie* case of obviousness, the U.S. Patent and Trademark Office must meet three basic elements:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Manual of Patent Examining Procedure, 8th ed., (M.P.E.P.) § 2142.

The combination of prior art references fails because it does not meet all elements of a *prima facie* case of obviousness. There is no teaching or suggestion in the '688 patent or Sad *et al.* to adminster an LHRH-diptheria toxoid conjugate in combination with an ionic polysaccharide to elicit an effective immune response to LHRH. Additionally, a skilled artisan would have had no reasonable expectation that administration of an LHRH-diptheria toxoid conjugate in combination with an ionic polysaccharide would elicit an effective immune response. Accordingly, the Examiner is using improper hindsight reconstruction in asserting that the prior art provided the requisite motivation to use an LHRH-diptheria toxoid conjugate in combination with an ionic polysaccharide to elicit an effective immune response to LHRH. *See In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988), *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

Amended independent claims 1 and 5 are directed to either a composition for use in eliciting an effective immune response to LHRH (claim 1) or a pharmaceutical composition (claim 5) comprising a LHRH-diptheria toxoid conjugate adsorbed to an ionic polysaccharide wherein said LHRH comprises a C-terminal fragment of at least five amino acids. The '688 patent and Sad *et al.* are cited as teaching LHRH-diptheria toxoid conjugates. The '688 patent also discloses 2-10 LHRH and Sad *et al.* further discloses the conjugates in alum as an adjuvant. The '487 patent is cited as teaching

the use of dextrans for the sustained release of biologically active polypeptides. The '586 patent is cited as teaching an LHRH conjugate (LHRH-TraTp) and suitable adjuvants, including DEAE-dextran, for the vaccination of animals and humans.

The '688 patent does not teach or suggest the use of a pharmaceutical composition comprising a LHRH diptheria toxoid conjugate for a contraceptive vaccine capable of inducing an effective immune response to LHRH. The '688 patent teaches a method of sterilizing an animal comprising administering an effective amount of a conjugate comprised of gonadotropin releasing hormone (GnRH) and a toxin. The chemical castration which is achieved by the method taught in the '688 patent results from the destruction of cells expressing GnRH receptors and not the induction of an immune response against the hormone.

Specifically, the '688 patent discloses the use of GnRH which has been conjugated to a toxic compound such that destruction of the gonadotrophs of an animal's anterior pituitary gland is effected by chemical attack. *See, inter alia,* '688 patent, abstract, col. 1, lines 15-18. The hormone-toxin conjugate binds to cells expressing a receptor directed to that hormone. Upon interaction of the hormone and the receptor, the presence of the hormone-linked toxic compound results in destruction of the cell expressing the receptor by virtue of the actions of the toxic compound. Accordingly, this process is one of chemical attack and destruction of cells in a directed manner. The '688 patent does not teach or suggest the instant invention because it discloses a means of destroying, by virtue of the induction of a toxic pathway, a subpopulation of cells expressing a receptor to a hormone of interest and not a means of inducing an immune response to the hormone itself. Thus, there is nothing that teaches or suggests that the method taught by the '688 patent would be useful for inducing an immune response to a suitably formulated hormone antigen.

Sad *et al.* actually teaches away from an LHRH-diptheria toxoid conjugate for use in eliciting an effective immune response to LHRH. A prior art reference must be considered as a whole, including portions that would teach away from the claimed invention. M.P.E.P. § 2141.02, *citing W. L. Gore & Assoc. v. Garlock, Inc.,* 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). Sad *et al.* discloses modulation of the immune response to GnRH. The subject modulation is induced by administering GnRH which is

linked to either diptheria toxoid or tetanus toxoid and is administered to a subject together with an alum adjuvant. Specifically, this reference demonstrates both stimulation *and* suppression of an immune response against GnRH. Sad *et al.* at page 225, right column, page 226, left column. These results would suggest to one of ordinary skill in the art that a significant proportion of an outbred population would fail to respond or respond poorly to an LHRH conjugate subunit type vaccine formulation, irrespective of the immunogenic protein and adjuvant which are used. Accordingly, Sad *et al.* neither teaches nor suggests any reasonable expectation of success in developing a highly efficacious LHRH vaccine using an LHRH-diptheria toxoid conjugate.

Neither of the primary references cited by the Examiner, the '688 patent and Sad *et al.*, provide any motivation to modify their teachings to arrive at the claimed invention and nothing in the secondary references, the '487 patent and the '586 patent, corrects this deficiency. "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not based on applicant's disclosure." M.P.E.P. § 2141 *citing In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The '487 patent discloses a sustained release pharmaceutical of a *drug*. By "sustained release" is meant that the drug which is formulated in this type of pharmaceutical is released in the recipient of the pharmaceutical in a gradual manner over a period of time. This provides many unique advantages including obviating the requirement that the drug is repeatedly administered. However, the notion of developing a formulation which achieves sustained release as would be required in relation to administering a therapeutic or prophylactic drug is completely distinct and unrelated to the notion of developing a formulation of a immunogen which induces an efficacious immune response. The former is aimed at delivering a molecule to a site of interest while the latter is directed to the significantly more complex process of stimulating a specific immune response.

The technology associated with achieving the gradual and sustained release of a drug is completely different to that involved in achieving the modulation of an immune response. Accordingly, although the Examiner states that dextran can be utilized to achieve the sustained release of virtually any biologically active polypeptide, the method

of the present invention is not directed to the sustained release of LHRH in the context described in the '487 patent, but instead to an LHRH formulation that can modulate the efficacy of an immune response.

The '586 patent discloses a novel LHRH fusion protein which is capable of eliciting a strong immune response to LHRH. The elicitation of this strong immune response and the very nature of the invention defined in the '586 patent, is the development of a TraTp-LHRH fusion protein which is highly immunogenic. The '586 patent teaches that the improvement in efficacy is due to the use of a TraTp-LHRH analog *per se* and not the nature of the formulation within which it is administered. The range of adjuvants listed to be suitable for use with this fusion protein is indicative of the fact that the improvement in efficacy is not due to the specific nature of the LHRH formulation, but rather is due to the nature of the LHRH fusion product. Further, nowhere in the document is it taught that of the large range of adjuvants, an ionic polysaccharide, such as DEAE-dextran, would produce a significantly more efficacious response if used together with a diptheria toxoid LHRH conjugate. That is, there are no teachings that the particular formulation which is claimed in the present application stands out from any other possible formulations which one may use in the context of eliciting an immune response directed to LHRH.

Without using the claimed invention and the present specification as the blueprint for hindsight picking and choosing the isolated elements of each of the cited references, one of ordinary skill in the art would have found no suggestion to modify the teachings of the '688 patent or Sad *et al.* in light of the teachings of the '487 patent and the '586 patent to meet the elements of the presently claimed invention. Furthermore, one of skill in the art would not have had a reasonable expectation that LHRH, when linked to diphtheria toxoid and administered together with an ionic polysaccharide, not only produces an efficacious result in a very high proportion of subjects, but produces a much more efficacious result than has been previously obtainable using any other prior art LHRH formulations.

Because the examiner has not established a prima facie case of obviousness, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-8.

CONCLUSION

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and arguments.

It is respectfully urged that the present application is now in condition for allowance. Early notice to that effect is earnestly solicited.

The examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. **(Amended)** A composition for use in eliciting an effective immune response to LHRH said composition comprising a LHRH-diptheria toxoid conjugate adsorbed to an ionic polysaccharide wherein said LHRH comprises a C-terminal fragment of at least five amino acids.

5. **(Amended)** A pharmaceutical composition comprising a LHRH-diptheria toxoid conjugate adsorbed to an ionic polysaccharide together with one or more pharmaceutically acceptable carriers and/or diluents wherein said LHRH comprises a C-terminal fragment of at least five amino acids.